Editorial on childhood asthma biomarkers including zinc: An exploratory cross-sectional study

Agrawal A. Childhood asthma biomarkers including zinc

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Abstract
In this editorial, we comment on the case-control study by Ibrahim et al published in the recent issue of the World Journal of Clinical Pediatrics 2023. Here, we have focused mainly on the difference in serum zinc levels between asthmatic children and healthy controls. Childhood bronchial asthma is a chronic inflammatory respiratory disease. It was found that an increase in oxidative stress leads to a decrease in antioxidants causing oxidative damage to mitochondrial respiratory chain complexes resulting in the inflammation of the airway, hypersecretion of mucus causing a cascade of clinical manifestations ranging from recurrent episodes of coughing, wheezing, and breathlessness to shortness of breath. Since oxidative stress mediates the inflammatory response in asthma, the supplementation of anti-oxidants can be one strategy to manage this disease. Zinc is one such antioxidant that has attracted much attention about asthma and airway inflammation. Zinc is a crucial trace element for human metabolism that helps to regulate gene expression, enzyme activity, and protein structure. Apart from zinc, free serum ferritin levels are also elevated in case of inflammation. Several previous studies found that ferritin levels may also help determine the pathology of disease and predict prognosis in addition to tracking disease activity. However, this study's results were different from the findings of the previous studies and the zinc
levels did not show a significant difference between asthmatic children and non-asthmatic children but ferritin levels were significantly high in asthmatic children as compared to the controls. Hence, the possible role of the biochemical nutritional assessment including zinc and ferritin as biomarkers for asthma severity should be assessed in the future.

**Key Words:** Asthma; Biomarker; Children; Zinc; Ferritin; Immunoglobulin E


**Core Tip:** Asthma is a chronic inflammatory disorder of the respiratory system, more common in children than adults. The disorder is the most common cause of emergency department visits, absenteeism from school, and hospitalization in children. The etiology of asthma is not clear but various triggering agents including environmental, nutritional, and genetic factors may have their roles. Previous studies found that trace elements with antioxidant properties such as zinc can be effective in the treatment of asthma. Apart from zinc, serum ferritin, and Ig E levels are also elevated in such children. Hence, further studies assessing these biomarkers are needed in the future.

**INTRODUCTION**

Bronchial asthma is a chronic inflammatory disease of the respiratory tract system affecting more than 300 individuals worldwide[1-3]. In children, asthma causes significant morbidity and mortality and its prevalence has been rising rapidly in recent times. Although the exact cause of asthma is unknown, several environmental and nutritional factors have an important role in triggering asthma[3]. In the case of inflammation, several immune cells are activated which release several harmful mediators such as reactive oxygen species and free radicals. An increase in oxidative stress leads to a decrease in antioxidants causing oxidative damage to mitochondrial
respiratory chain complexes. This damage causes inflammation of the airway, hypersecretion of mucus, contraction of smooth muscle, and epithelial shedding resulting in limitation of the air to the lungs causing a cascade of clinical manifestations ranging from recurrent episodes of coughing, wheezing, and breathlessness to shortness of breath. It was also found that different cytokines and chemokines contribute to the pathogenesis of asthma\[^2\].

Since oxidative stress mediates the inflammatory response in asthma, the supplementation of anti-oxidants can be one of the strategies to manage this disease. It was discovered that a decline in the dietary intake of antioxidants contributes to the increased incidence of asthma. Among all antioxidants, zinc has garnered attention about asthma and airway inflammation due to its immune-modulating properties. Zinc is a crucial trace element that contributes to the maintenance of the immune system, growth and development, oxidative stress, tissue repair and regeneration, and inflammatory reactions\[^1\]. It is the second most abundant trace metal in the human body after iron which is present in the approximate concentration of 2-4 g. The disruption of zinc homeostasis causes Th1/Th2 balance to shift towards a Th2 response, which leads to a hyper-inflammatory response, a fundamental abnormality in asthma\[^3\].

Furthermore, zinc is a crucial part of antioxidant enzymes, which are needed to prevent the creation of free radicals, which are thought to exacerbate asthma\[^4\]. Due to its antioxidant and anti-apoptotic effects and the presence of several growth co-factors, zinc safeguards the respiratory system and contributes to the synthesis of proteins, DNA, as well as, RNA, the production of energy, and the growth of the cell. Hence, a decreased dietary intake of anti-oxidant substances or increased consumption of oxidative substances may raise the incidence and severity of asthma. In addition to zinc, the levels of free serum ferritin tend to rise in case of inflammation as it has a protective role in redox biology and iron homeostasis. Immunoglobulin E acts as a highly sensitive immunological amplifier by triggering rapid pathological reactions and recognizing antigens.
In the recent issue of the *World Journal of Clinical Pediatrics*, an interesting article titled ‘Childhood asthma biomarkers including zinc: An exploratory cross-sectional study’ has been published. It is a case-control study carried out at the Children’s Hospital, Cairo University, investigating children with bronchial asthma ($n = 40$) and healthy children ($n = 21$). Data on sociodemographic and clinical characteristics such as body mass index and degree of asthma severity were collected. The study addresses an important issue wherein the effect of serum zinc levels on bronchial asthma was assessed. Additionally, other laboratory parameters such as serum ferritin and IgE levels, were studied. They found that the mean $\pm$ SD serum zinc level for asthmatic vs non-asthmatic children was 94.4 $\pm$ 24.7 and 85.2 $\pm$ 19, respectively, with no significant difference. Similarly, no significant differences were observed regarding serum iron, Hb, and albumin levels in cases vs controls. In contrast, serum levels of IgE and ferritin showed significant differences between cases and controls ($P = 0.001$ and 0.006, respectively).

In line with this study, a meta-analysis conducted by Ghaffari *et al* found that there was no significant difference between the standard mean differences in zinc levels among asthmatic children as compared to the control group. Elsayed *et al* found higher mean serum zinc levels among asthmatic children than in the healthy group. In contrast to the present study, Abdelaziz *et al* showed a significant improvement in decreasing the frequency of attacks ($P = 0.036$), nocturnal symptoms ($P < 0.001$), clinical control of asthma symptoms ($P < 0.001$) after 8 wk of zinc supplementation and a significant improvement was found in pulmonary functions in forced expiratory volume in 1 s ($P < 0.001$) and forced vital capacity ($P = 0.002$). Another study conducted by Abdul Wahab *et al* also showed a positive correlation between serum zinc levels and bronchial asthma in children.

In a meta-analysis of 21 articles including 2205 children, Xue *et al* found a statistically significant association between circulating zinc and risk for childhood asthma and wheezing. These conflicting results between this study and the other studies may be explained by the differences in study designs, genetic, and
environmental differences among the participants. It was found that the frequency of zinc deficiency is higher in Middle Eastern countries, mainly due to the presence of high concentrations of dietary phytates in cereals and legumes\textsuperscript{[8]}. The presence of phytates in beans, unrefined grains, and nuts is the main reason for the inhibition of dietary zinc absorption resulting in its deficiency. Hence, pre-existing zinc deficiency in children can be correlated with the diverse study results between the studies.

The strength of this study was the assessment of not only zinc but also the levels of serum ferritin, as well as, IgE among asthmatic children. Also, the sample size is adequate for a clinical study. In our view, a few limitations exist in this study as they have not assessed the relationship between serum zinc levels and the severity of asthma. They have assessed only the relationship between these two parameters but not in terms of disease severity. Also, on what basis the children were classified as mild, moderate, and severe asthmatic was not specified.

**CLINICAL IMPLICATIONS**

Zinc is a potent immunomodulator and an important cofactor of more than 2000 transcription factors and more than 300 enzymes which helps to maintain the oxidative balance in the body by maintaining various cellular processes such as cell proliferation, differentiation, apoptosis, DNA and RNA synthesis, tissue maintenance, immune function, and glucose and lipid metabolism. This anti- and pro-oxidative balance is disrupted in asthma which can be maintained using zinc supplements. Due to these properties, it has been used as a medication for various allergic diseases like chronic rhino-sinusitis and atopic dermatitis\textsuperscript{[9]}. Zinc supplements have been shown to reduce the nocturnal exacerbation of asthma, wheezing, cough, and other symptoms in children with bronchial asthma\textsuperscript{[6,10,11]}. The use of zinc supplements decreases antibiotic consumption and the incidence of respiratory tract infection, particularly in children. Hence, the patients and their parents need to be educated about the importance of zinc in their diet.
FUTURE PERSPECTIVES

Zinc dyshomeostasis has been linked with several lung diseases including asthma. The comparison of zinc levels among asthmatics and healthy children can help to formulate the exact role of zinc among such patients. With further and more extensive studies on varied populations, a gold standard value of appropriate zinc level can be obtained. The zinc levels below this value can be considered a risk factor for bronchial asthma. However, more research on zinc homeostasis is required which could pave the way for new therapeutics targeting the use of zinc supplementation in inflammatory lung diseases.

CONCLUSION

In conclusion, we can say that zinc contributes to many biological functions and acts as an anti-inflammatory, antioxidant, antiviral agent, and immunomodulator. Zinc supplementation can be used for treating various respiratory diseases including asthma. However, the correlation between asthma and zinc levels among asthmatic children is not found significant in this study. We need more studies with bigger sample sizes and powerful methodology to confirm this relationship. Even though these studies do not have powerful methodologies; zinc supplementation could be effective in the prevention and treatment of asthma in children as an additive.

REFERENCES


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